

Multitarget therapy versus intravenous cyclophosphamide in the induction treatment of lupus nephritis: a metaanalysis of randomized controlled trials

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Background/aim: Multitarget therapy for lupus nephritis (LN) remains in its exploratory phase and the recent evidence is insufficient. This study aimed to evaluate the efficacy and safety of mycophenolate mofetil (MMF), tacrolimus (TAC), and steroids (multitarget therapy) versus intravenous cyclophosphamide (IVC) and steroids in induction treatment of LN.

Materials and methods: We searched for randomized controlled trials of MMF plus TAC versus IVC in LN using PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the China Biology Medicine Database, and the China National Knowledge Infrastructure Database. We assessed the retrieved citations and selected studies according to predefined inclusion and exclusion criteria.

Results: In total, we identified 8 trials including 801 patients. The metaanalysis revealed that overall multitarget therapy is more effective at inducing complete renal remission compared with IVC (RR: 1.94, 95% CI: 1.61–2.33; $P < 0.00001$). In terms of LN classification, multitarget therapy exhibited superiority compared with IVC for inducing complete remission of class IV LN (RR: 1.52, 95% CI: 1.10–2.08; $P = 0.01$), class V LN (RR: 4.24, 95% CI: 1.30–13.88; $P = 0.02$), and class V+IV LN (RR: 2.29, 95% CI: 1.45–3.62; $P = 0.0004$); however, no superiority was noted for class III LN or class V+III LN. The rates of gastrointestinal symptoms, abnormal liver function, leukopenia, and irregular menstruation were significantly reduced in the multitarget therapy group compared with the IVC group for LN. Nevertheless, the multitarget therapy group more frequently exhibited new-onset hypertension compared with the IVC group.

Conclusion: Multitarget therapy is more effective than IVC in the induction treatment of LN in Chinese patients and exhibits a better safety profile.

Key words: Lupus nephritis, cyclophosphamide, mycophenolate mofetil, tacrolimus, metaanalysis.

1. Introduction

Lupus nephritis (LN) remains a common complication of systemic lupus erythematosus (SLE); it has a considerable influence on patient outcomes and is associated with a sixfold increase in mortality compared with the general population (1,2). The main goals of treating LN are to induce renal remission and to prevent renal flares and end-stage renal disease. Patients with complete remission exhibit better clinical outcomes compared with patients with partial remission and especially patients who do not respond to treatment (3,4). The use of immunosuppressive drugs has improved the remission rates and long-term renal survival in recent decades. The combination of corticosteroids and cyclophosphamide (CYC) and/or mycophenolate mofetil (MMF) is recommended as the current induction therapy for LN; however, the complete

remission rate remains inadequate (5–10). Previous studies demonstrated that the remission rate of patients with class V+IV LN was only 21%–27% with the CYC treatment regimen (11,12). Under treatment with MMF or tacrolimus (TAC), patients with class V+IV LN obtained a complete remission rate of only 20% to 21.1% (13, 14). Moreover, adverse effects such as amenorrhea, hemorrhagic cystitis, sepsis, and malignancy events exhibited high rates (15). To identify a more effective and safer therapy, Liu et al. (16) proposed and studied multitarget therapy, the combination of MMF, TAC, and steroids, for LN induction treatment. Multitarget therapy exhibited a significantly increased complete remission rate at 24 weeks (45.9%) compared with intravenous cyclophosphamide (IVC) (25.6%). Furthermore, adverse events were observed less frequently in the multitarget therapy group. Multitarget therapy has

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also been utilized in the treatment of both proliferative and membranous LN (17,18). Currently, increasing research emphasizes the role of multitarget treatment for LN (19–21). However, these studies included a small sample size and the pathological classes of patients varied. Therefore, we performed this metaanalysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of multitarget therapy versus IVC as induction therapy in different LN pathological classes.

2. Materials and methods

2.1. Inclusion criteria

Two authors assessed studies for inclusion in this metaanalysis based on the following criteria: 1) the study involved patients who had been diagnosed with SLE according to the criteria of the American College of Rheumatology and biopsy-proven LN class III, IV, V, V+III, or V+IV according to the ISN/RPS 2003 classification; 2) the study compared the efficacy and safety of TAC plus MMF with IVC; and 3) it was a RCT. Retrospective studies and non-RCTs were excluded.

2.2. Search strategy

We searched PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the China Biology Medicine Database (CBM), and the China National Knowledge Infrastructure Database (CNKI) (all to May 2017) without any restrictions. The search terms ‘lupus nephritis’, ‘tacrolimus’ and ‘mycophenolate mofetil’ and their related terms were employed. We assessed the reference lists of all included studies to identify other potentially relevant trials.

2.3. Study selection

Two authors separately examined the titles and abstracts of all retrieved studies and excluded studies that clearly did not meet the inclusion criteria. The full texts of studies that appeared to meet the inclusion criteria or were uncertain were searched. Then two authors assessed these studies independently to establish whether they could be included. In cases of disagreement, a third author was asked to give an opinion to resolve the issue.

2.4. Data extraction and management

Two authors independently extracted information on the study design, baseline characteristics of patients, intervention and control treatment, outcome data, and definitions of outcomes from studies. In cases of missing data, we contacted the original authors to obtain the required information. Any differences in data extraction were resolved by discussion.

2.5. Study quality assessment

The quality of included studies was evaluated using the Cochrane Handbook (22). The risk of bias comprised a

description and judgment based on the following criteria: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other source of bias. Each criterion was judged as ‘Low risk of bias’, ‘Unclear risk of bias’, or ‘High risk of bias’. Two authors separately evaluated the quality of the included studies. In cases of disagreement, consensus was reached by discussion.

2.6. Statistical analysis

Statistical analyses were performed with Cochrane RevMan 5.3 (23). The risk ratio (RR) and 95% confidence interval (CI) were calculated for dichotomous data. The mean difference (MD) and 95% CI were used to report continuous data. Clinical heterogeneity was assessed by considering the design of each study. If no clinical heterogeneity was observed, statistical heterogeneity was evaluated using the chi-square test ($P < 0.1$ indicates significance) and quantified using the I^2 statistic (I^2 value $> 50\%$ indicates significant heterogeneity) (22). If heterogeneity did not exist among studies, a fixed-effect model was utilized. If significant statistical heterogeneity was noted, a random-effects model was utilized instead of the fixed-effect model, which was employed for studies that appeared to be clinically and methodologically homogeneous. Subgroup analysis was planned to explore the treatment effects for different LN pathological classes.

3. Results

3.1. Study selection

Our electronic search identified 579 studies, including 489 in English and 90 in Chinese. In total, 535 studies, including duplicate references, reviews, basic research, meeting abstracts, case reports, and non-RCTs, were excluded after title and abstract examination. The full texts of the remaining 24 articles were retrieved for further review. Finally, eight eligible citations (16–21,24,25), including two in English and six in Chinese, were included in the metaanalysis (Figure 1).

3.2. Study characteristics and quality assessment

The baseline characteristics of the included studies are summarized in Table 1 and the risks of bias are presented in Figure 2. These eight studies involved a total of 801 patients, including 671 female patients. In total, 406 patients were treated with multitarget therapy and 395 were treated with IVC. All of the included studies provided a statement regarding randomization; however, only four studies explained random sequence generation that was computer-generated (16,17,19,25). Four trials reported withdrawals and dropouts (16–19). The main study limitation was a failure to explain blinding or the lack of a double-blind design.

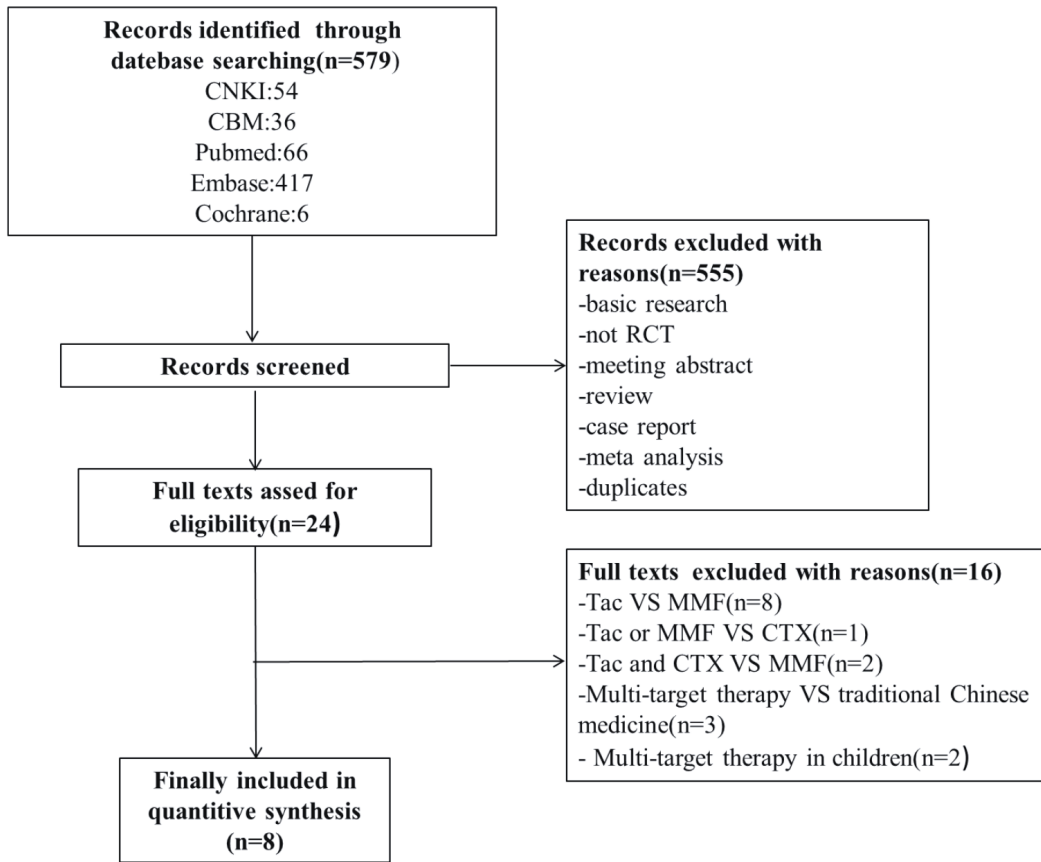


Figure 1. Study selection flowchart.

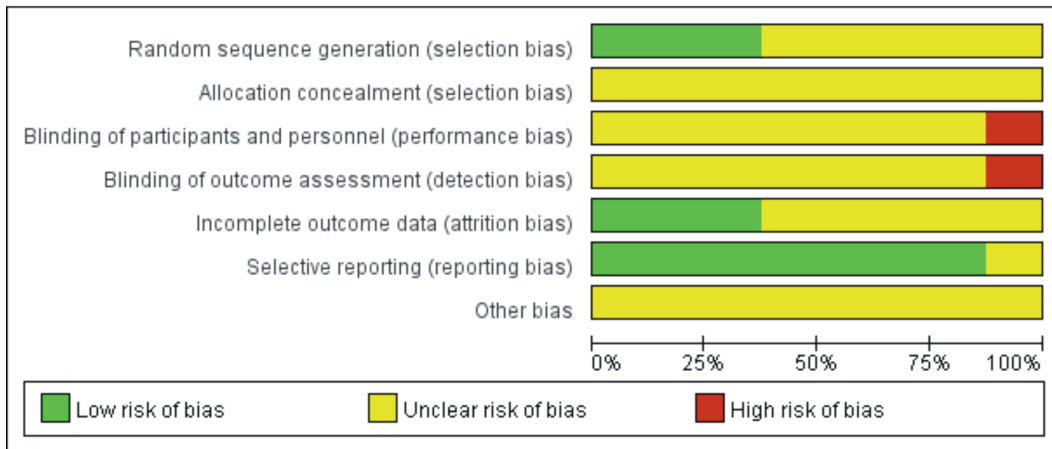


Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.3. The efficacy of multitarget therapy versus IVC for LN

The complete remission rate was reported in all eight trials. No significant heterogeneity was noted among studies; thus, the fixed-effect model was used. Based on the metaanalysis results, the complete remission rate of the multitarget group was significantly increased

compared with the IVC group (RR: 1.94, 95% CI: 1.61–2.33; $P < 0.00001$) (Figure 3). Subgroup analysis revealed that multitarget therapy was superior to IVC for inducing a complete remission of class IV LN (RR: 1.52, 95% CI: 1.10–2.08; $P = 0.01$) and class V LN (RR: 4.24, 95% CI: 1.30–13.88; $P = 0.02$) and significantly superior for class

Table 1. Baseline characteristics of included studies.

Characteristic	Bao et al., 2008 (17)	Hu et al., 2011 (18)	Li, 2014 (24)	Liu et al., 2015 (16)	Zhang et al., 2016 (25)	Zhao and Xu, 2016 (19)	Huang et al., 2017 (20)	Jiang et al., 2017 (21)
Sex (M/F)	M: 4/16 C: 2/18	M: 6/39 C: 4/30	M: 19/9 C: 18/10	M: 23/168 C: 20/161	M: 11/19 C: 10/20	M: 3/47 C: 4/46	M: 3/13 C: 2/14	M: 5/31 C: 6/30
Age (years)	M: 25.2 ± 8.9 C: 30.6 ± 4.6	M: 25.1 ± 9.4 C: 30.5 ± 8.9	M: 35.2 ± 5.4 C: 35.2 ± 5.4	M: 30.3 (23.3–38.6) ‡ C: 33.6 (24.2–41.5) ‡	M: 30.4 ± 12.8 C: 30.6 ± 12.7	M: 31.2 ± 10.3 C: 33.2 ± 11.6	M: 35.8 ± 13.9 C: 35.6 ± 13.6	M: 29.1 ± 5.5 C: 28.7 ± 5.3
Urine protein (g/24 h)	M: 4.41 ± 1.95 C: 4.10 ± 1.20	M: 3.5 ± 2.0 C: 3.6 ± 2.0	Unclear	M: 3.44 (2.24–5.49) ‡ C: 3.68 (2.41–5.38) ‡	Unclear	M: 5.10 ± 3.16 C: 4.92 ± 2.20	M: 3.92 ± 0.64 C: 3.97 ± 0.55	M: 4.94 ± 2.12 C: 5.01 ± 2.55
Serum creatinine (mg/dL)	M: 0.87 ± 0.21 C: 0.89 ± 0.30	M: 0.82 ± 0.26 C: 0.86 ± 0.35	Unclear	M: 0.77 (0.63–1.04) ‡ C: 0.82 (0.64–1.05) ‡	Unclear	M: 1.49 ± 1.03 C: 1.52 ± 0.76	Unclear	M: 1.07 ± 0.20 C: 1.06 ± 0.19
Serum albumin (g/L)	M: 23.9 ± 5.7 C: 24.6 ± 3.9	M: 30.7 ± 6.5 C: 28.8 ± 6.5	Unclear	M: 26.0 (21.5–30.7) ‡ C: 25.1 (20.1–31.0) ‡	Unclear	M: 23.3 ± 3.86 C: 22.1 ± 4.37	M: 26.8 ± 6.4 C: 27.2 ± 5.8	M: 25.76 ± 6.97 C: 26.11 ± 7.22
Anti-dsDNA Positive [n (%)]	M: 12 (60) C: 12 (60)	M: 17 (37.7) C: 13 (38.2)	Unclear	M: 106 (59.2) C: 113 (63.1)	Unclear	M: 34 (68.0) C: 33 (66.0)	M: 14 (87.5) C: 13 (81.3)	M: 23 (63.89) C: 24 (66.67)
Serum C3 <0.79g/L [n (%)]	M: 20 (100) C: 19 (95)	M: 0.59 ± 0.26† C: 0.53 ± 0.23†	Unclear	M: 0.44 (0.34–0.62) ‡ C: 0.43 (0.34–0.63) ‡	Unclear	M: 0.65 ± 0.13† C: 0.66 ± 0.06†	Unclear	M: 0.61 ± 0.18† C: 0.58 ± 0.11†
Pathologic class [n (III/IV/V+III/V+IV)]	M: 0/0/0/0/20 C: 0/0/0/0/20	M: 0/18/0/11/16 C: 0/13/0/9/12	Unclear	M: 10/74/32/19/46 C: 9/76/37/7/52	Unclear	T: 5/41/16/6/17§	M: 1/8/2/1/4 C: 2/7/2/2/3	M: 15/13/8/0/0 C: 13/14/9/0/0
SLE-DAI	M: 14.9 ± 4.0 C: 14.0 ± 2.4	Unclear	Unclear	M: 16.0 (12.0–18.0) ‡ C: 15.0 (12.0–18.0) ‡	Unclear	M: 16.0 ± 5.9 C: 17.0 ± 4.1	M: 16.2 ± 5.4 C: 15.7 ± 5.8	M: 15.50 ± 3.25 C: 16.22 ± 4.11
Duration	9 months	9 months	9 months	24 weeks	24 weeks	9 months	36 weeks	6 months

Table 1. (Continued).

Characteristic	Bao et al., 2008 (17)	Hu et al., 2011 (18)	Li, 2014 (24)	Liu et al., 2015 (16)	Zhang et al., 2016 (25)	Zhao and Xu, 2016 (19)	Huang et al., 2017 (20)	Jiang et al., 2017 (21)
Treatment regimen	M: TAC 3–4 mg/day, maintain a blood concentration within 5–7 ng/mL, MMF 0.75–1 g/day, maintain AUC from 0 to 12 h of MPA at 20–45 mg h/L C: IVC 0.5–1 g/m ² monthly for 6–9 months. All patients received MP pulse therapy followed by oral prednisone	M: TAC 4 mg/day, maintain a blood concentration within 4–7 ng/mL, MMF 1 g/day, maintain AUC from 0 to 12 h of MPA at 20–30 mg h/L C: IVC 0.5–1 g/m ² monthly for 6–9 months All patients received MP pulse therapy followed by oral prednisone	M: TAC 4 mg/day, MMF 1 g/day C: IVC was initiated at a dose of 0.75 g/m ² and maximum dose less than 1.2 g monthly for 6–9 months All patients received MP pulse therapy followed by oral prednisone	M: TAC 4 mg/day, MMF 1g/day C: IVC 0.5–1 g/m ² monthly for 24 weeks All patients received MP pulse therapy followed by oral prednisone	M: TAC (2–4 mg/day), MMF (0.5–1 g/day) C: IVC 8–12 mg/kg monthly for 24 weeks All patients received MP pulse therapy followed by oral prednisone	M: TAC 0.15 mg/kg daily, MMF 50 mg/kg daily C: IVC 0.8–1 g monthly for 9 months All patients received MP pulse therapy followed by oral prednisone	M: TAC (3–4 mg/day), maintain a blood concentration within 5–7 ng/mL, MMF (0.75–1 g/day) C: IVC 0.5–1 g/m ² monthly for 24–36 weeks All patients received MP pulse therapy followed by oral prednisone	M: TAC (3–4 mg/day), maintain a blood concentration within 10 ng/mL, MMF (0.75–1 g/day), maintain AUC from 0 to 12 h of MPA within 45 mg h/L C: IVC 0.5–1 g/m ² monthly for 6 months All patients received MP pulse therapy followed by oral prednisone
Definition of complete remission	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range or not >15% more than baseline values	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range or not >15% more than baseline values	Proteinuria <0.3 g/24 h with normal urinary sediment, serum albumin normal serum creatinine range	Proteinuria <0.3 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range or not >15% more than baseline values	Proteinuria <0.4 g/24 h with normal urinary sediment, serum albumin ≥35 g/L, normal serum creatinine range

Values expressed as M ± SD. To convert creatinine value to mg/dL, multiply by 0.0113. M, Multitarget therapy group; C, cyclophosphamide group; T, total; SLE-DAI, Systemic Lupus Erythematosus Disease Activity Index. †Values expressed as M ± SD. ‡Values expressed as number (percentage), median (25th–75th percentiles). §Values include pathologic class II, 15 cases.

M, Multitarget therapy group; C, cyclophosphamide group; AUC, area under the time concentration curve; MP, methylprednisolone; AZA, azathioprine; MPA, mycophenolate acid.

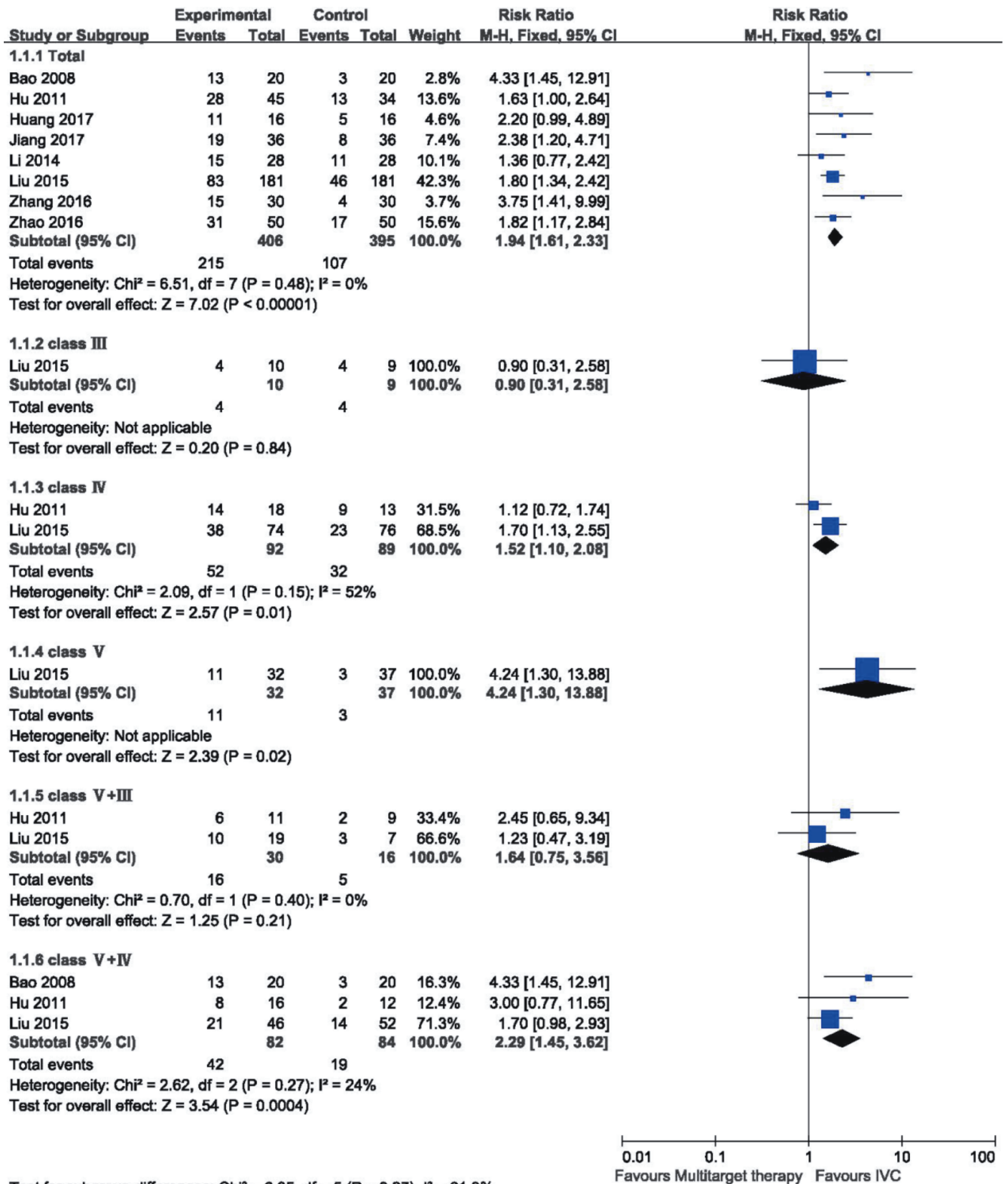


Figure 3. Forest plot of the effects of multitarget therapy versus IVC on complete remission rate in different pathological LN classes.

V+IV LN (RR: 2.29, 95% CI: 1.45–3.62; P = 0.0004); however, superiority was not observed for class III and class V+III LN (Figure 3).

Two trials reported the changes in urine protein and serum albumin after treatment. Multitarget therapy significantly reduced urine protein (MD: -1.07, 95% CI: -2.01 to -0.13; P = 0.03) (Figure 4) and increased serum albumin (MD: 1.96, 95% CI: 0.63–3.29; P = 0.004) (Figure 5) compared with IVC. No obvious heterogeneity was noted between these studies.

The anti-dsDNA negative conversion rates and serum C3 normalization rates were reported by four studies and

one study, respectively. Based on the metaanalysis results, the anti-dsDNA negative conversion rate of the multitarget group was significantly increased compared with that of the IVC group (RR: 1.55, 95% CI: 1.06–2.26; P = 0.02) and only one group reported serum C3 normalization rates (RR: 1.31, 95% CI: 0.68–2.53; P = 0.43) (Figure 6). No obvious heterogeneity was noted between these studies.

3.4. The safety of multitarget therapy versus IVC for LN
The results of adverse events comparing multitarget therapy with IVC are presented in Table 2. No significant heterogeneity was noted among studies as evaluated by the I² statistic of 0% or 53% and thus the fixed-effect model

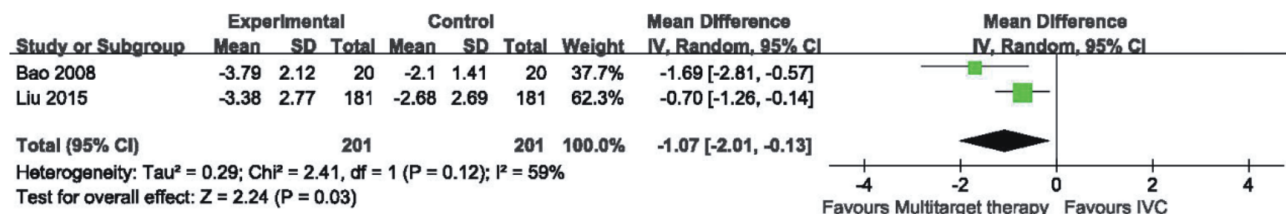


Figure 4. Forest plot of the effects of multitarget therapy versus IVC on urine protein in LN.

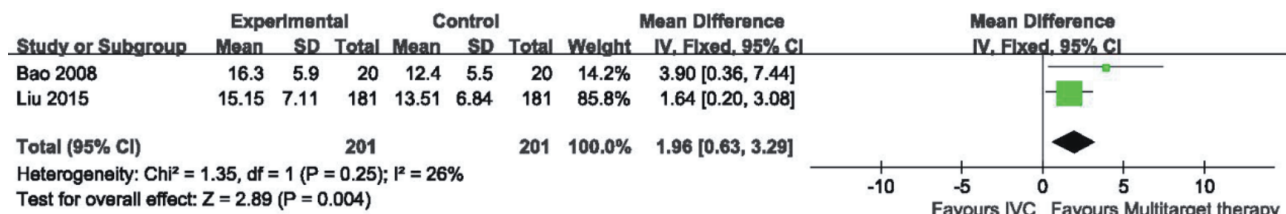


Figure 5. Forest plot of the effects of multitarget therapy versus IVC on serum albumin in LN.

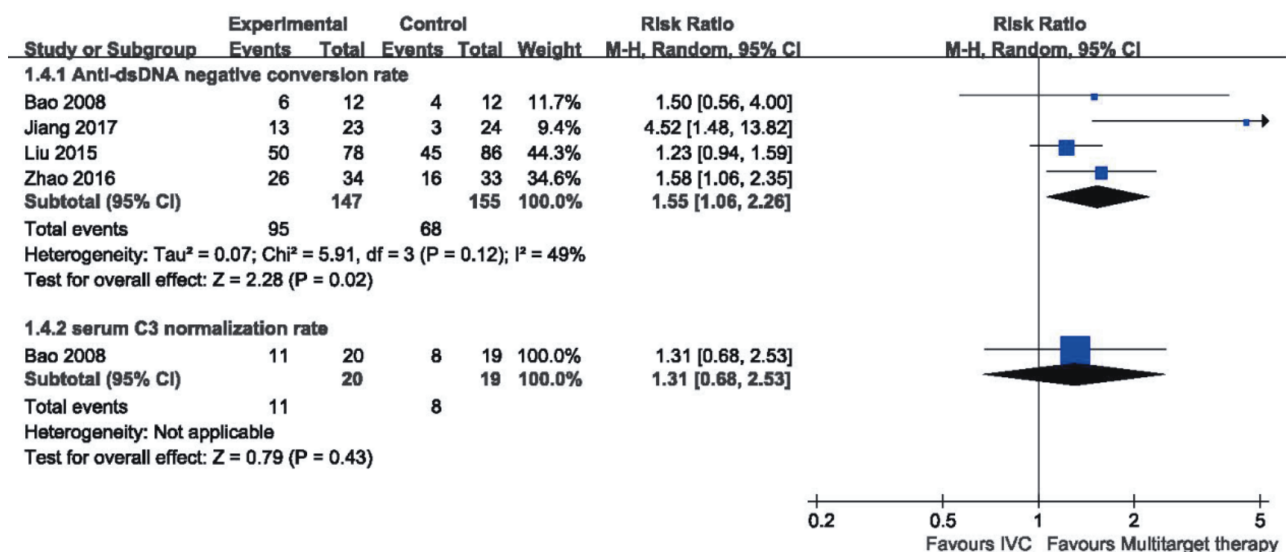


Figure 6. Forest plot of the effects of multitarget therapy versus IVC on anti-dsDNA negative conversion rate and serum C3 normalization rate in LN.

was used. The metaanalysis results indicated that the rates of gastrointestinal symptoms, abnormal liver function, leukopenia, and irregular menstruation were significantly reduced in the multitarget therapy group compared with the IVC group. The rates of infection, alopecia, and hyperglycemia were similar between the two groups. However, the multitarget therapy group more frequently exhibited new-onset hypertension compared with the IVC group.

4. Discussion

LN renal lesions vary from minimal lesions to advanced sclerosis, which may lead to end-stage renal disease. The optimal choice for treating LN should consider the pathological class and severity (26). The combination of corticosteroids and CYC and/or MMF is recommended as the current induction therapy for LN (5–7). A previous study demonstrated that the role of MMF is not clear in treating LN and it should not be recommended as the induction drug for severe LN (27). Thus, treating the severe pathological class of LN remains challenging. Immune dysregulation is fundamental to the pathogenesis of LN, as both B and T cells are involved in the development of the disease. MMF, a lymphocyte-selective antiproliferative agent, has proven to be an effective and safe therapy in LN in a number of RCTs (28–30) and metaanalyses (31,32). TAC, a T cell-specific calcineurin inhibitor, has emerged as an effective and safe immunosuppressive drug for treating LN (33–35). MMF plus TAC has been used in organ transplantation patients for years (36) and is a useful therapy for early mixed cellular and humoral renal allograft rejections (37). Liu et al. (16) demonstrated that multitarget therapy for LN is more effective than a single agent. The publication of their results inspired a new wave of relevant research (19–21,25). To better understand the

efficacy and safety of multitarget therapy versus IVC as induction therapy in different LN pathological classes, the present metaanalysis with subgroup analysis was performed.

The main finding based on this metaanalysis is that multitarget therapy exhibits significant superiority compared with IVC for inducing complete remission of LN, particularly V+IV. However, no superiority was noted for class III and class V+III LN. The rates of gastrointestinal symptoms, abnormal liver function, leukopenia, and irregular menstruation were significantly reduced in the multitarget therapy group compared with those of the IVC group for LN. The rates of infection, alopecia, and hyperglycemia were similar between groups. However, the multitarget therapy group exhibited new-onset hypertension more frequently than the IVC group. Moreover, multitarget therapy significantly reduced urine protein, increased serum albumin, and significantly increased the anti-dsDNA negative conversion rate compared with the IVC group.

There are several limitations to this metaanalysis. First, only one or two studies were included in some subgroup analyses. Thus, the findings should be regarded with caution and more large-scale RCTs are needed to confirm these results. Second, the included studies mostly were small-scale and no trial was double-blinded. Third, the participants in the included studies were exclusively Chinese. The efficacy and safety of multitarget therapy for LN in other races should be proven in further studies. Finally, the included studies reported the short-term outcomes of induction treatment; thus, the long-term efficacy and toxicity of multitarget therapy for LN patients must be proven by further long-term studies.

Our metaanalysis of current RCTs suggested that multitarget therapy is more effective than IVC for

Table 2 Metaanalysis of adverse events.

Outcomes	Studies	Multitarget therapy	IVC	Heterogeneity (P, I ²)	RR	95% CI	P-value
Gastrointestinal symptoms	7	42/376	82/365	0.05, 53%	0.51	0.37–0.71	<0.0001
Abnormal liver function	6	11/362	25/351	0.68, 0%	0.44	0.23–0.86	0.02
Leukopenia	7	11/376	34/365	0.31, 16%	0.33	0.18–0.63	0.0006
Infection	7	125/378	133/367	0.35, 10%	0.93	0.78–1.11	0.42
Irregular menstruation	5	6/279	18/265	0.84, 0%	0.36	0.16–0.84	0.02
Alopecia	5	11/332	21/321	0.78, 0%	0.52	0.26–1.05	0.07
Hyperglycemia	3	7/246	6/235	0.54, 0%	1.09	0.39–3.02	0.87
New-onset hypertension	5	23/304	6/293	0.88, 0%	3.14	1.40–7.04	0.006

IVC, Intravenous cyclophosphamide; RR, relative risk; CI, confidence interval. RR < 1 favors multitarget therapy; RR > 1 favors IVC group.

inducing a complete remission of LN, especially for class V+IV Chinese patients, and exhibits a better safety profile. Further large-scale high-quality RCTs are needed to confirm these results.

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